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SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR TREATMENT OF PSORIASIS AND PSORIATIC ARTHRITIS

This application claims the benefit of provisional patent applications U.S. Serial Number 60/130,074, filed April 19, 1999, U.S. Serial Number 60/134,320, filed May 14, 1999, U.S. Serial Number ____, filed July 19, 1999, and U.S. Serial Number _____, filed August 11, 1999.

FIELD OF THE INVENTION

The invention pertains to methods for treating psoriatic arthritis and psoriasis by administering a TNFα antagonist, such as recombinant TNFR:Fc.

BACKGROUND OF THE INVENTION

Psoriatic arthritis (PsA) is a disease entity that shares some features with both rheumatoid arthritis (RA) and the inflammatory skin disease psoriasis (for review, see Breathnach, In Klippel and Dieppe eds. *Rheumatology*, 2nd Ed., Mosby, 1998, 22.1-22.4). Psoriasis is a chronic autoimmune dermatologic condition characterized by epidermal keratinocyte hyperproliferation, and which is accompanied by neutrophil and T cell infiltration. The etiology of psoriasis remains unclear, though one proposal is that it involves a genetic predisposition that causes keratinocytes to abnormally proliferate in response to cytokines locally produced by T lymphocytes present in the dermis (Ameglio et al., *Clin Lab Invest* 189:359-363, 1994; Austin et al., *J Dermatol Sci* 16 (suppl. 1): S1777, 1998). Among the cytokines found at elevated levels in psoriatic lesions are tumor necrosis factor (TNFα), IL-6 and TGFβ, molecules that often are associated with inflammation (e.g., Bonifati et al., *Clin Exp Dermatol* 19:383-387, 1994).

Psoriatic skin lesions, which occur in about 1-3% of the general population, are present in patients who suffer from PsA. The incidence of PsA is variably reported to occur in 6-42% of patients with psoriatic lesions (Gladman, *Rheum Dis Clin NA*. 18:247-256, 1992). While ordinary psoriasis in its acute phases may be accompanied by joint pain, this pain is relatively mild and transient and does not involve the often deforming degeneration of joints and bone that occurs in patients who have PsA. For example, in several large studies of patients with PsA, 40-57% had erosive arthropathy, about 17% had ≥5 deformed joints, 11-19% were disabled, and in a group followed for 5 years, the

proportion with ≥5 damaged joints doubled (Alonso et al., *J Rheum* 30:245-250, 1991; Gladman et al., *Quart J Med* 62:127-141, 1987; Gladman et al., *J Rheumatol* 17:809-812, 1990).

Psoriasis has no cure and individuals often must experiment with different therapies to find one that effectively controls their symptoms. Treatments that sometimes are effective include topical medications (e.g., steroids, coal tar, anthralin, vitamin D3 and its analogs, sunshine, topical retinoids), phototherapy (e.g., ultraviolet light, photochemotherapy (PUVA), and internal medications (e.g., methotrexate, systemic steroids, oral retinoids, cyclosporine, or a rotating regimen of these three). In addition, it has been proposed that psoriasis could be treated with quinolinesulfonamides, catechol diether compounds, isoxazoline compounds or mercapto alkyl peptidyl compounds, all of which inhibit either the production of TNFα or its release from cultured cells (U.S. 5,834,485, U.S. 5,563,143, U.S. 5,869,511 and U.S. 5,872,146).

Psoriasis and PsA are different clinical entities, e.g., they are associated with somewhat different MHC haplotypes (Gladman, 1992; Breathnach, 1998), and the overall prognosis for the latter is far worse than for the former. Nonetheless, treatments used for the psoriatic lesions of PsA generally are similar to those used to treat psoriasis.

Some investigators have proposed that overproduction of tumor necrosis factor (TNFα), a cytokine often associated with inflammation, contributes to the pathology of psoriasis (e.g., Pigatto et al., *J Invest Dermatol* 94:372-376, 1990; Sagawa et al., *Dermatol* 187:81-83, 1993; Ameglio et al., *Dermatol* 189:359-363, 1994), but other reports cast doubt on this hypothesis. For example, while one group found that cultured mononuclear cells from psoriasis patients produced more TNFα than cells from control patients (Mizutani et al., *J Dermatol Sci* 14:145-153, 1997), another group performing similar studies reported no differences (Kapp et al, *Br J Dermatol* 122:587-592, 1990). In another study, elevated levels of serum TNFα were observed during the active phase of a severe form of psoriasis, but normal levels were seen in a control group of psoriasis patients, i.e., patients with a less severe form of the disease (see Table 1, Seishima et al., *Dermatol* 196:371-372, 1998). In a study that used immunohistological techniques, similar levels of TNFα were reported in the epidermis of psoriasis and control patients, and no change in TNFα levels was noted following treatment (Oxholm, *APMIS* 100 (Suppl. 24):5-32, 1992; see page 21). Others observed similar serum TNFα levels in

psoriasis patients and controls, and noted no change in psoriatic patients' TNFα levels following various therapies (Tigalonova et al., *Acta Derm Venereol (Stockh)* Suppl 186:25-27, 1994). In contrast, other groups have reported that TNFα levels present in serum or lesion suction blister fluids not only are elevated in psoriasis patients, but that they decreased concomitantly with lesion regression during treatment (e.g., Ameglio et al., 1994; Mussi et al., *J Biol Regul Homeost Agents* 11:115-118, 1997; Chodorowska, *J Eur Acad Dermatol Venerol* 10:147-151, 1998).

The role of TNFα in psoriasis remains unsettled. One group reported some improvement in a group of psoriasis patients treated with pentoxifylline, a drug that can inhibit the release of TNFα, but which exerts many of its physiological effects by inhibiting cyclic AMP phosphodiesterase (Omulecki et al., *J Am Acad Dermatol* 34:714-715, 1996; Centola et al., *J Androl* 16:136-142, 1995; Elferinck et al., *Biochem Pharmacol* 54:475-480, 1997). Both psoriasis and PsA have been associated with a polymorphism in the TNFα promoter (Höhler et al., *J Invest Dermatol 109*:562-565, 1997). Some studies have suggested that TNFα mitigates psoriasis. For example, one study showed that TNFα upregulated the expression of manganese superoxide dismutase, an enzyme believed to protect tissues from the toxic effects of superoxide radicals generated during inflammation (Löntz et al., *Free Radical Biol Med* 18:349-355, 1995), while other studies have shown that TNFα inhibits the growth of cultured keratinocytes (e.g., Malkani et al., *Exp Dermatol* 2:224-230, 1993). Another study showed that TNFα serum levels in psoriasis patients increased during the late phase of cyclosporine treatment, though it decreased during etretinate treatment, even though lesions improved equally with either treatment (Shiohara et al., *J Am Acad Dermatol* 27:568-574, 1992). In studies with nude mice, TNFα injections corrected the hyperproliferation of engrafted human psoriatic skin (Gilhar et al., *Clin Exp Immunol* 106:134-142, 1996). Some studies have shown that TNFα itself is effective for treating psoriasis, resulting in lesion diminution, as well as decreased joint swelling and improved motion (Takematsu et al., *Br J Dermatol* 124:209-210, 1991; Creaven et al., *J Am Acad Dermatol* 24:735-737, 1991).

In addition to psoriatic lesions, PsA is characterized by distal interphalangeal joint (DIP) involvement, enthesopathy, spondylitis and dactylitis. The psoriatic nail lesions of PsA typically involve a characteristic pitting or abnormal ridging pattern. The

histopathogenesis of PsA and the more well-studied RA are similar in some ways. In both RA and in active PsA, patients exhibit increased levels of HLA-DR$^+$ T cells and MHC class II antigens in their synovial membranes and synovial fluid, as well as increased expression of the cytokine TNFα. In addition, both diseases also are associated with prominent synovial vascular changes.

The discovery of rheumatoid factor in the serum of RA patients provided an important tool for differentiating PsA from RA, but the realization that RA and PsA are distinct diseases was based primarily on their many clinical differences (Helliwell and Wright, *In* Klippel and Dieppe eds. *Rheumatology*, 2nd Ed., Mosby, 1998, 21.1-21.8). Prominent clinical features of PsA include the frequent involvement of phalangeal joints, an accompanying sacroiliitis, and a characteristic mutilating arthritis with reduction in bone stock, particularly in the digits (telescoping digits). PsA is distinguished from RA also by radiographic appearance, a notably higher degree of synovial membrane vascularity as well as differences in the levels of various cytokines in the synovial fluids (Ritchlin et al., *J Rheumatol* 25:1544-52, 1998; Veale et al., *Arth Rheum* 36:893-900, 1993). Veale et al. noted differences in synovial membrane adhesion molecules and numbers of macrophages when they compared RA and PsA patients, as well as observing a minimal degree of hyperplasia and hypertrophy of synoviocytes in PsA as compared with RA patients. Because of such differences, coupled with the association of PsA but not RA with class I MHC antigens, Ritchlin et al. have suggested that PsA must be triggered by different mechanisms than those underlying RA. Veale et al. suggested for similar reasons that different cytokines were likely to be interacting in the synovium of PsA and RA patients.

A number of studies have investigated cytokine levels associated with PsA. One study demonstrated that unusually high levels of Il-6 and Il-8 were released from PsA patients' peripheral lymphocytes following contact with activated cultured endothelial cells (Dunky et al., *Clin Immunol Immunopath* 85:297-314, 1997), and another study showed that levels of TNFα, Il-1β, Il-8 as well as TNF receptors in synovial fluids were higher in PsA patients than in OA patients, though they were lower than in RA patients (Partsch et al., 1997; Partsch et al., *J Rheumatol* 25:105-110, 1998; Partsch et al., *Ann Rheum Dis* 57:691-693, 1998).

Most of the drugs used for treating the arthritic aspects of PsA are similar to those used in RA (Salvarini et al., *Curr Opin Rheumatol 10*:229-305, 1998). The so-called "first-line" drugs are the non-steroidal antiinflammatories (NSAIDs), which may be used alone or in combination with the second-line disease-modifying anti-rheumatic drugs, or "DMARDs". DMARDs currently used include methotrexate, sulfasalazine, gold, azathioprine, cyclosporine, antimalarials, steroids and colchicine, as well as many others that are used less frequently. However, one group found that methotrexate, which is widely used for treating PsA, failed to slow the progression of joint damage in PsA patients after being administered for 24 months (Abu-Shakra et al., *J Rheumatol* 22:241-45, 1995), and another group reported very little improvement in PsA patients who had received methotrexate (Willkens et al., *Arthr Rheum* 27:376-381, 1984). Similarly, Clegg et al. found only a slight improvement over placebo in PsA patients treated with sulfasalazine (Clegg et al., *Arthritis Rheum* 39: 2013-20, 1996). Some studies have indicated that the immunosuppressor cyclosporine is effective in treating PsA (reviewed in Salvarini et al., 1998), though this drug has severe side effects. In addition, others have proposed that psoriatic arthritis could be treated with truncated TNFα receptors or with a combination of methotrexate and antibodies against TNFα (WO 98/01555; WO 98/0537).

Recently, Jones et al. performed a comprehensive meta-analysis of a number of PsA treatment studies, and concluded that PsA and RA differed not only in their response to treatment with specific drugs, but in the relative magnitudes of improvement in the placebo arms of the studies (Jones et al., *Br J Rheumatol* 36:95-99, 1997). As an example, PsA patients responded better gold salt therapy than did RA patients, though the gold did not affect the PsA patients' psoriatic skin lesions (Dorwart et al., *Arthritis Rheum* 21:515-513, 1978). As discussed above, others have noted a variety of differences between PsA and RA and have concluded on this basis that different underlying factors or mechanisms probably exist for these two diseases (Veale et al., 1993; Ritchlin et al., 1998).

SUMMARY OF THE INVENTION

Provided are methods for treating psoriatic arthritis and psoriasis by administering an antagonist of TNFα, such as soluble recombinant TNFR receptor, for a period of time sufficient to induce a sustained improvement in the patient's condition.

DETAILED DESCRIPTION OF THE INVENTION

Provided are methods of treating psoriatic arthritis (PsA) and psoriasis that involve administering to a human patient having PsA or psoriasis a therapeutically effective amount of an antagonist of human TNFα, particularly with a soluble protein that prevents TNFα from binding to its natural cell-bound receptor. TNFα, a pleiotropic cytokine associated with inflammation, binds to cells through two membrane receptor molecules having molecular weights of approximately 55 kDa and 75 kDa (p55 and p75). In addition to binding TNFα, these same receptors mediate the binding to cells of TNFβ (often called "LTα"), another cytokine associated with inflammation. LTα shares structural similarities with TNFα (Cosman, *Blood Cell Biochem* 7:51-77, 1996). In some embodiments of the invention, the TNFα antagonist is a molecule that is capable of inhibiting the binding of TNFα to a TNFα receptor (TNFR).

In some embodiments of the invention, the soluble TNFα antagonist mimics a soluble TNFR in that the antagonist is capable of binding TNFα molecules, and thereby inhibits TNFα from binding to its natural receptors on the cell. For purposes of the methods disclosed herein, a soluble molecule that comprises all or part of a TNFR and that binds TNFα is a "TNFR mimic." In some instances, the TNFR mimic also binds LTα, thus preventing LTα from interacting with its cell-bound receptors. The soluble TNFR mimics of the present invention may be derived from TNFRs p55, p75 or fragments thereof. Soluble TNFR molecules used to construct TNFR mimics include, for example, analogs or fragments of native TNFRs having at least 20 amino acids, that lack the transmembrane region of native TNFR, and that are capable of binding TNFα. TNFα binding or LTα binding can be assayed using ELISA or any other convenient assay. In one embodiment of the invention, the soluble TNFR polypeptides or fragments are fused with a second polypeptide to form a chimeric protein. The second polypeptide may one that promotes the spontaneous formation by the chimeric protein of a dimer, trimer or higher order multimer that is capable of binding a TNFα and/or LTα molecule and preventing it from binding to cell-bound receptors.

A TNFR mimic suitable for treating PsA or psoriasis in accord with the invention is the human recombinant TNFα antagonist TNFR:Fc, a term which as used herein refers to "etanercept," which is a dimer of a chimeric protein molecule derived from the

extracellular portion of the p75 TNFα receptor, each molecule consisting of a 235 amino acid polypeptide that is fused to a 232 amino acid Fc portion of human IgG_1. Etanercept is a recombinant protein currently sold by Immunex Corporation under the trade name ENBREL,® and it has been used successfully to treat rheumatoid arthritis (RA) (Weinblatt et al., *New Eng J Med* 340:253-259, 1999). Etanercept competes for TNFα with the receptors on the cell surface, thus inhibiting TNFα from binding to the cell. It may be relevant to the potency of etanercept *in vivo* that the p75 receptor protein that it incorporates binds not only to TNFα, but also to the inflammatory cytokine LTα. Thus, etanercept can act as a competitive inhibitor of LTα. In addition to etanercept, the invention provides for the treatment of PsA and psoriasis with other TNFR mimics that comprise all or part of the extracellular portion of p75 or p55.

In certain embodiments of the invention, the TNFα antagonist, such as a TNFR mimic, is administered concurrently with antagonists of inflammatory cytokines, including but not limited to antagonists of TGFβ, IFNγ, Il-1, Il-6 or Il-8.

For purposes of this invention, patients are defined as having PsA if they have one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails. The psoriatic lesions may appear before or after the onset of swollen or tender joints. It is understood that prior to treatment, manifestations of PsA may have persisted over time, e.g., for several months or years, and may involve several joints. According to one classification system (reviewed in Alonso et al., 1991), PsA patients can be categorized based on their arthritic symptoms into five clinical subgroups: 1) DIP; 2) mutilans arthritis; 3) symmetrical polyarthritis; 4) oligoarticular arthritis; and 5) ankylosing spondylitis-like. The disclosed methods are suitable for treating all five forms of PsA.

Patients are defined as having psoriasis if they do not have PsA but have one of the following: 1) inflamed swollen skin lesions covered with silvery white scale (plaque psoriasis or psoriasis vulgaris); 2) small red dots appearing on the trunk, arms or legs (guttate psoriasis); 3) smooth inflamed lesions without scaling in the flexural surfaces of the skin (inverse psoriasis); 4) widespread reddening and exfoliation of fine scales, with or without itching and swelling (erythrodermic psoriasis); 5) blister-like lesions (pustular psoriasis); 6) elevated inflamed scalp lesions covered by silvery white scales (scalp psoriasis); 7) pitted fingernails, with or without yellowish discoloration, crumbling nails,

or inflammation and detachment of the nail from the nail bed (nail psoriasis). Any of the above-described types of lesions may appear in a patient who has PsA, with nail lesions being particularly prevalent.

A therapeutically effective amount of a TNFα antagonist is considered to be an amount that results in an improvement in the patient's condition as measured according to any indicator that reflects the severity of the patient's PsA or psoriasis. One or more such indicators may be assessed for determining whether the amount of TNFα antagonist and duration of treatment is sufficient. The baseline value for the chosen indicator or indicators is established by examination of the patient prior to administration of the first dose of the etanercept or other TNFα antagonist. An improvement over baseline in the patient's condition is obtained by administering one or more doses of a soluble molecule that reduces TNFα levels in the skin, serum or synovial fluids.

In some embodiments of the invention, a TNFR mimic, such as TNFR:Fc, is administered to a PsA patient in an amount and for a time sufficient to induce an improvement over baseline in one or more than one of the following indicators that serves as measures of the severity of the patient's disease: joint swelling; joint pain or tenderness; patient self-assessment; physician assessment; psoriasis area and severity index (PASI); or Target Lesion Assessment score, which is an index for assessing the severity of individual skin lesions. Measurements of PASI score or Target Lesion Assessment score also are suitable for assessing the sufficiency of treatment when a TNFR mimic is used to treat psoriasis. A single dose may be administered, or the TNFR mimic may be administered repeatedly.

A satisfactory degree of improvement is obtained by administering the TNFR mimic, such as TNFR:Fc, one time, two times or three or more times per week. Treatment may be continued over a period of at least one week, or if deemed advisable by the patient's physician, for two weeks, three weeks, four weeks or longer, or for an indefinite period of time. In many cases, an improvement in the patient's condition will be noted after treatment has been administered for at least one or two weeks, or even after a single dose has been administered.

When used as an indicator of treatment sufficiency, patient self-assessment or physician assessment may be measured, for example, on a subjective numerical scale in which one extreme of the scale represents "no disease," and the other extreme indicates

"severe disease" (i.e., a "Likert" scale). Either extreme of the scale may be used to represent "no disease." Such a scale can have any desired range of numerical values, e.g., 0-3, 0-4, 0-5, 0-6, 0-7, etc., and provides a basis for comparison to the patient's condition at baseline. A 0-3 point system, for example, could involve the following categories: 0=no disease; 1=mild disease; 2=moderate disease; 3=severe disease. In this example, a patient would be regarded as "improved" if their score decreased by one category. As used herein, the term "Likert scale" is understood to include visual analog scales (VAS), in which a patient or physician circles a number that they feel best represents the patient's status with respect to the parameter being measured. If a patient's score worsens as compared with their baseline score, the change in their Likert score is assigned a negative value.

A soluble TNFR mimic, such as TNFR:Fc, administered in accord with this invention may be administered concurrently with one, two, three or more other medications used to treat PsA or psoriasis. These additional medications may be administered simultaneously with the TNFR mimic and one another, or may be administered at different times. Drugs suitable for concurrent administration include pain medications that include but are not limited to acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol. In addition, the TNFR:Fc or other TNFR mimic may be administered concomitantly with a disease-modifying anti-rheumatic drug (DMARD), including but not limited to methotrexate, sulfasalazine, gold salts, azathioprine, cyclosporine, antimalarials, steroids (e.g., prednisone) and colchicine. Anti-inflammatories may also be coadministered with the TNFR mimic. Such anti-inflammatories include but are not limited to: aspirin; ibuprofen; indomethacin; celecoxib; rofecoxib; ketorolac; nambumetone; piroxicam; naproxen; oxaprozin; sulindac; ketoprofen; diclofenac; and other COX-1 and COX-2 inhibitors, salicylic acid derivatives, propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, carboxylic acid derivatives, butyric acid derivatives, oxicams, pyrazoles and pyrazolones, including newly developed antiinflammatories that are effective for treating arthritic joints. Moreover, the TNFR:Fc may be administered concomitantly with other kinds of agents that are used to treat PsA, including but not limited to: antibodies directed against T-cell surface proteins; oral retinoids, including etretinate; minocycline, misoprostol, oral collagen, penicillamine, 6-mercaptopurine,

nitrogen mustard, gabapentin, photochemotherapy, psoralen combined with ultraviolet A (PUVA), bromocriptine, somatostatin, interferon gamma, plasmapheresis, peptide T, anti-CD4 monoclonal antibody, fumaric acid, 1,25-dihydroxy vitamin D3, polyunsaturated ethyl ester lipids, zinc or fish oil; and other drugs that may be used to treat psoriasis. It is understood that the response by individual patients to the aforementioned medications may vary, and the most efficacious combination of drugs for each patient will be determined by his or her physician.

In one embodiment of the invention, a sufficient amount and time of treatment for PsA will occur when the treatment has induced an improvement according to the American College of Rheumatology (ACR) criteria as modified by Felson et al. (Felson et al., *Arthritis Rheum* 6:727-735, 1995). When ACR criteria are used, the treatment is considered to be sufficient when the patient has improved by at least 20% (ACR20) or by at least 50% (ACR50) in both tender joint count (ca. 78 joints assessed) and swollen joint count (ca. 76 joints assessed), and also shows an improvement in three of the following five: 1) subject pain assessment; 2) subject global assessment; 3) physician global assessment; 4) subject self-assessed disability; 5) acute-phase reactant (Westergreen erythrocyte sedimentation rate or C-reactive protein level). Of the preceding five criteria, the first four are scored on a Likert scale. Subject and global assessments are determined based on the overall status of the patient's disease.

In yet another embodiment of the invention, the amount and time of treatment for either PsA or psoriasis is considered to be sufficient when the treatment has induced an improvement in the patient's psoriasis area and severity index (PASI index). In one embodiment, the treatment is regarded as sufficient when the patient exhibits an at least 50% improvement in his or her PASI score, and in another embodiment, when the patient exhibits an at least 75% improvement in PASI score.

In other embodiments of the invention, the sufficiency of treatment for PsA or psoriasis is determined by evaluating individual psoriatic lesions for improvement in severity (Psoriasis Target Lesion Assessment Score), and continuing treatment until an improvement is noted according to this scoring system. This scoring system involves determining for an individual lesion whether improvement has occurred in plaque elevation, amount and degree of scaling or degree of erythema, and target lesion response to treatment, each of which is separately scored. Psoriasis Target Lesion Assessment

Score is determined by adding together the separate scores for all four of the aforementioned indicia.

Although a patient's degree of PsA or psoriasis after treatment may appear improved according to one or more of the above-discussed indices, it should be understood that treatment with TNFR:Fc or other TNFR mimic may be continued after the patient has shown improvement, and may be continued indefinitely if deemed advisable by the patient's physician.

A TNFR mimic in accord with the invention, such as TNFR:Fc, may be administered to a psoriasis patient or a PsA patient concomitantly with one, two, three or more other treatments used to treat psoriasis. Such treatments include, but are not limited to: topical steroids; systemic steroids; anthralin; topical coal tar; vitamin D3 and its analogs; topical retinoids; sunshine; moisturizers; salicylic acid; phototherapy with ultraviolet light B; psoralen combined with ultraviolet light A (PUVA); methotrexate; oral retinoids; cyclosporine; hydroxyurea; and sulfasalazine. It is understood that the response by individual patients to the aforementioned medications or treatments may vary, and the most efficacious combination of drugs for each patient will be determined by his or her physician.

For treating PsA or psoriasis, any efficacious route of administration may be used to therapeutically administer TNFR:Fc or other TNFR mimic. The TNFR:Fc or other TNFR mimic can be administered, for example, via intra-articular, intravenous, intramuscular, intraperitoneal or subcutaneous routes by bolus injection, continuous infusion, sustained release from implants, or other suitable techniques. In some instances, the TNFR:Fc or TNFR mimic may be administered by routes other than by injection, e.g., by aerosol, orally or by other means as may be desired. Soluble TNFα antagonists according to the invention also may be administered in a sustained-release form. Sustained-release forms of TNFα antagonists suitable for use in the disclosed methods include, but are not limited to, TNFR:Fc that is encapsulated in a slowly-dissolving biocompatible polymer, TNFR:Fc that is admixed with such a polymer, and TNFR:Fc that is encased in a biocompatible semi-permeable implant. In addition, the TNFR mimic may be conjugated with polyethylene glycol (pegylated) to enhance protein delivery. Alternatively, soluble TNFRs may be administered by implanting cultured cells that express the protein, for example, by implanting cells that express the TNFR:Fc protein.

In one embodiment, the patient's own cells are induced to produce TNFR:Fc by transfection *in vivo* or *ex vivo* with a DNA that encodes the TNFR:Fc protein. This DNA can be introduced into the patient's own cells, for example, by injecting naked DNA or liposome-encapsulated DNA that encodes TNFR:Fc, or by other means of transfection.

Typically, the TNFR mimic is administered in the form of a composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers should be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the TNFR mimic, such as TNFR:Fc, with buffers, antioxidants such as ascorbic acid, low molecular weight polypeptides (such as those having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. Preferably, the TNFR mimic is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages for these various formulations can be determined in standard dosing trials, and may vary according to the route of administration that is chosen. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

TNFR:Fc or other TNFR mimics for treating PsA or psoriasis preferably are administered for at least one time per week. In one embodiment of the invention, TNFR:Fc is administered one time per week, in another it is administered two times per week, and in another embodiment, it is administered three times a week.

If administered by injection, an effective amount of TNFR:Fc may range from 1-20 mg/m^2, and preferably is about 5-12 mg/m^2. Alternatively, a flat dose may be administered, whose amount may range from 5-100 mg/dose. An exemplary range for a flat dose is about 20-30 mg per dose. In one embodiment of the invention, a flat dose of 25 mg/dose of TNFR:Fc is administered by injection at least one or more times per week. If a route of administration other than injection is used, the dose is appropriately adjusted in accord with standard medical practices.

In addition to PsA and psoriasis, elevated levels or abnormal expression of TNFα also have been observed in a number of other diseases and pathologic conditions. In various embodiments of the invention, diseases associated with pathological manifestations of TNFα are treated by the administration of a soluble TNFR mimic, such as TNFR:Fc, as disclosed herein. Such conditions treatable with TNFR:Fc include, but are not limited to: acne, including but not limited to acne rosacea; graft-versus-host disease; aplastic anemia (acquired and Fanconi's); myelofibrosis; the myelodysplastic syndromes (MDS), including refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia; cancer, including but not limited to multiple myeloma, hairy cell leukemia, acute myelogenous leukemia, chronic or acute lymphoblastic leukemia, adenocarcinoma (e.g., breast, ovarian, stomach, colon), and solid tumors (e.g., to inhibit angiogenesis), malignancies with invasive metastatic potential; cancer-associated cachexia, fatigue and asthenia; polymyositis; dermatomyositis; tenosynovitis; juvenile rheumatoid arthritis; Still's disease; uveitis associated with rheumatoid arthritis; Reiter's disease; polymyalgia rheumatica; Sjogren's syndrome; ankylosing spondylitis; rejection of kidney transplants in diabetic recipients; autoimmune hearing loss; myocardial infarction; congestive heart failure; cachexia of heart failure; complications of coronary bypass surgery; Wegener's granulomatosis; giant cell arteritis; thrombophlebitis; stroke; benign prostatic hypertrophy (BPH) and prostatitis; chronic pelvic pain, including chronic prostatitis/pelvic pain syndrome; endometriosis; fetal loss syndrome or IV embryo loss (spontaneous abortion); allergic asthma; allergic rhinitis; obesity-mediated insulin resistance; multiple sclerosis; Alzheimer's disease; Parkinson's disease; dementia; chronic fatigue syndrome; chronic pain; low back pain; Bell's palsy; sarcoidosis; dermatomyositis; scleroderma; loss of skin elasticity; alopecia areata; toxic epidermal necrolysis; chronic pancreatitis; Crohn's disease; gastric and duodenal ulcers; idiopathic gastroparesis; chronic periodontitis; osteoporosis, including post-menopausal osteoporosis; idiopathic pulmonary fibrosis; systemic lupus erythematosus; trauma; ischemia resulting from reperfusion injury; autoimmune heart disease; pneumonitis; psoriasis, including psoriatic arthritis; inflammatory skin disease; atopic dermatitis; Kawasaki's vasculitis; liver inflammation; chronic hepatitis C; acute alcoholic hepatitis; acquired immunodeficiency syndrome (AIDS), including AIDS associated wasting;

amyloidosis; Kaposi's sarcoma; Gaucher's disease; Creuztfeld-Jacob disease; cerebral malaria; schistosomiasis; tuberculosis, including pulmonary tuberculosis; neurogenic pain; post-herpetic pain; myasthenia gravis; Il-2 toxicity; inflammatory eye diseases; solid organ transplantation; diabetic retinopathy; non-insulin dependent diabetes; autoimmune juvenile onset diabetes; autoimmune sclerosing cholangitis; restenosis after heart surgery; loosening of prosthesis after joint replacement or orthopedic implant osteolysis; adult respiratory distress syndrome; hyperimmunoglobulin D and periodic fever syndrome; and Meniere's disease.

In one aspect of the invention, the treatment of various diseases or pathologic conditions associated with abnormal or elevated TNFα expression, including each of those listed above, is accomplished by administering TNFR:Fc to a patient in an amount and for a time sufficient to induce a sustained improvement in at least one indicator that is known to reflect the severity of the patient's disease or pathologic condition. Any efficacious route of administration may be used, including but not limited to injection, sustained release formulations, aerosol inhalation, eyedrops, oral preparations, including pills, syrups, lozenges or chewing gum, and topical preparations such as lotions, gels, sprays, ointments or the like. For example, TNFR:Fc may be injected by intra-articular, intravenous, intralesional, intramuscular, intraperitoneal or subcutaneous routes by bolus injection or continuous infusion.

In one embodiment of the invention, TNFR:Fc is administered to adults one time per week to treat the above indications, in another preferred embodiment is administered two times per week, and in another preferred embodiment is administered three or more times per week. In some instances, a single injection may suffice to induce an improvement in the patient's condition. If injected, the effective amount of TNFR:Fc per adult dose ranges from 1-20 mg/m^2, and preferably is about 5-12 mg/m^2. Alternatively, a flat dose may be administered, whose amount may range from 5-100 mg/dose, or a flat dose of about 20-30 mg per dose may be used. In one embodiment of the invention, a flat dose of 25 mg/dose is administered to an adult human patient by subcutaneous injection two times or three times per week. If a route of administration other than injection is used, the dose is appropriately adjusted in accord with standard medical practices. For pediatric patients (age 4-17), one exemplary regimen is the subcutaneous injection of 0.4 mg/kg, up to a maximum dose of 25 mg of TNFR:Fc, administered one time per week,

two times per week or three or more times per week as described above. In another preferred embodiment, a dose of 25 mg of TNFR:Fc is administered to an adult patient by subcutaneous injection two times a week or three times per week for at least three weeks.

It should be understood that the duration of TNFR:Fc administration for any of the indications described herein can vary, and its administration may be continued indefinitely if this is deemed advisable by the patient's physician. Dose adjustments may be made by the patient's physician in accord with the medical needs of individual patients, and other medications used to treat the same conditions may be administered concurrently.

In addition to human patients, a patient treated with TNFR:Fc may be a non-human animal, such as a pet (dogs, cats, birds, primates, etc.), domestic farm animal (horses cattle, sheep, pigs, birds, etc.), or any animal that suffers from a TNFα-mediated inflammatory or arthritic condition. In such instances, an appropriate dose may be determined according to the animal's body weight. For example, a dose of 0.2-1 mg/kg may be used. Alternatively, the dose is determined according to the animal's surface area, an exemplary dose ranging from 0.1-20 mg/m^2, or more preferably, from 5-12 mg/m^2. For small animals, such as dogs or cats, a suitable dose is 0.4 mg/kg. TNFR:Fc, or another soluble TNFR mimic, is administered by injection or other suitable route one or more times per week until the animal's condition is improved, or it may be administered indefinitely. In some instances, a non-human patient is treated with a soluble recombinant TNFR mimic that is constructed from genes derived from the same species as the patient.

The following example is provided to illustrate the advantages of various embodiments of the invention, and is not intended in any way to limit the scope of the disclosure.

EXAMPLE

Evaluation of TNFR:Fc in Patients with Psoriatic Arthritis.

Sixty patients with active psoriatic arthritis (PsA) were enrolled in a Phase II double-blind, randomized, placebo controlled study to determine whether the subcutaneous biweekly administration of etanercept (recombinant TNFR:Fc) was safe in this patient population and whether efficacy could be documented for both the arthritic and psoriatic aspects of this disease.

In this study, a flat dose of 25 mg of TNFR:Fc was injected subcutaneously two times a week. After 12 weeks, patients who completed the study were eligible for continuation into a 24 week open-label extension of the study, with assessments made at weeks 16, 36 and 30 days post-study. All patients participating in the study extension received etanercept, including those patients who had received placebo during the blinded portion of the study.

In order to qualify for enrollment, subjects had to have at least one of the following forms of PsA: 1) DIP involvement; 2) polyarticular arthritis, absence of rheumatoid nodules and presence of psoriasis; 3) arthritis mutilans; 4) asymmetric peripheral arthritis; or 5) ankylosing spondylitis-like PsA. Subjects furthermore had to exhibit three or more swollen joints and three or more tender or painful joints at the time of enrollment, and to have exhibited an inadequate response to NSAID therapy. Subjects who were on other medications, including methotrexate, NSAIDs or oral corticosteroids were permitted to continue these other treatments at the same dose so long as the investigator considered these other treatments to inadequately control the patient's disease. Methotrexate was concurrently taken by 47% of the etanercept group, and 47% of the placebo group, NSAIDs were concurrently taken by by 67% of the etanercept and 77% of the placebos and oral corticosteroids by 40% of the etanercept and 20% of the placebo patients. Pain medications, including acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol, also were permitted during the study, as well as the use of topical tar compounds.

To qualify as having PsA, patients had to have experienced at least one psoriatic lesion of the skin or nails. Patients were evaluated at baseline (day 1 of treatment) as follows: 1) complete joint assessment; 2) psoriasis assessment; 3) duration of morning stiffness; 4) health assessment (quality of life) questionnaire, visual analog scale (HAQ/VAS); 5) patient global assessment; 6) erythrocyte sedimentation rate (ESR, Westergren); 7) C-reactive protein (CRP); and 8) urinalysis. At weeks 4 and 8, patients were evaluated as follows: 1) complete joint assessment; 2) psoriasis assessment; 3) duration of morning stiffness; 4) HAQ/VAS; 5) patient global assessment. At the end of 12 weeks, subjects were evaluated as follows: 1) complete joint assessment; 2) psoriasis assessment; 3) focused physical exam;

4) duration of morning stiffness; 5) HAQ/VAS; 6) patient global assessment; 6) hematology profile; 7) chemistry profile; 8) ESR; 9) CRP; 10) urinalysis; 11) serum tested for antibody to TNFR:Fc. Only those patients whose psoriasis was stable and covered ≥3% of body area were evaluated for psoriasis response during this trial, although patients whose psoriasis was inactive or covered less area were permitted to enroll.

A primary endpoint for clinical improvement or worsening of PsA was the Psoriatic Arthritis Response score, which is a composite score based on the following four measures: 1) patient self-assessment; 2) physician assessment; 3) joint pain or tenderness; 4) joint swelling. Both self- and physician assessments, i.e., overall assessment of disease status, were measured according to a five point Likert scale, in which a patient was considered as "improved" if his or her score decreased by one category, or as "worse" if his or her score increased by one category. Joint pain or tenderness was measured on a 5-point scale, wherein 1 = none and 5 = severe (withdrawal on examination). Joint swelling was evaluated on a 4-point scale in which 1 = none; 2 = mild (detectable synovial thickening without loss of bony contour); 3 = moderate (loss of distinctness of bony contours); and 4 = severe (bulging synovial proliferation with cystic characteristics). For this last measure, a decrease in swelling of ≥30% was scored as an "improvement," and an increase in swelling of ≥30% was scored as a "worsening." Patients were classified as "improved" under the Psoriatic Arthritis Response scoring system if they exhibited an improvement in at least two of the four measures described above, provided that one of the improved areas was joint pain or joint tenderness, and where there was no worsening in any of the four measures.

In addition, a secondary endpoint used for assessing psoriatic arthritis was a modified version of the American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis (modified ACR 20 response) (Felson et al., 1995). To qualify as "improved" according to this measure, a patient must have exhibited ≥20% improvement in both tender joint count (78 joints assessed) and swollen joint count (76 joints assessed), and also must have shown an improvement in

three of the following five: 1) subject pain assessment; 2) subject global assessment; 3) physician global assessment; 4) subject self-assessed disability; 5) acute-phase reactant (Westergreen erythrocyte sedimentation rate or C-reactive protein level). The joint count was done by scoring several different aspects of tenderness, such as pressure and joint manipulation on physical examination, wherein each joint was scored as "tender" or "nontender." Similarly, each joint is scored after physical examination as "swollen" or "not swollen." The subject's pain assessment was based on a horizontal visual analog scale (usually 10 cm) or Likert scale. The subject's and physician's global assessments of the subject's current disease status was based on an anchored horizontal visual analog scale (usually 10 cm), or Likert scale response. The subject's self-assessment of disability was based on any of the following measures, all of which have been validated in RA trials: Arthritis Impact Measurement Scale (AIMS); Health Assessment Questionnaire ; the Quality (or Index) of Well Being Scale; the McMaster Health Inventory Questionnaire (MHIQ); and the McMaster-Toronto Arthritis patient preference questionnaire (MACTAR).

A primary endpoint used to assess the psoriatic aspects of PsA was the standard psoriasis area and severity index (PASI) (Fredriksson and Petersson, *Dermatologica* 157:238-244, 1978). For this study, a positive treatment response was defined as an at least 50% or an at least 75% improvement in a patient's PASI score. For assessing area and severity, the body is divided into four regions: head (10%); trunk (30%); upper extremities (20%); and lower extremities (40%). Each quadrant also was scored for the severity of erythema (E), infiltration (I) and desquamation (D), using a four point scale, in which 0=no symptoms present; 1=slight symptoms; 2=moderate symptoms; 3=striking symptoms; 4=exceptionally striking symptoms. Using a 6-point scale, each region was scored also for the percent of total area that was involved in the psoriatic manifestations of the disease, wherein 0=no involvement; 1=<10% involvement; 2=10-<30% involvement; 3=30-<50% involvement; 4=50-<70% involvement; 5=70-<90% involvement; 6=90-100% involvement. PASI scores were calculated according to the formula given below, in which E=severity score for erythrema, I=severity score for infiltration, D=severity score for desquamation and A=total area involved. In this formula, the letters "h," "t," "u" and "l" represent, respectively, the scores in each of the four body regions, i.e., head, trunk, upper extremities and lower extremities. The PASI

score varies in steps of 0.1 units from 0.0 (no psoriatic lesions at all) to 72.0 (complete erythroderma of the severest possible degree).

PASI= 0.1(Eh+Ih+Dh)Ah + 0.3(Et+It+Dt)At + 0.2(Eu+Iu+Du)Au + 0.4(El+Il+Dl)Al

A secondary endpoint used for the psoriatic aspect of psoriatic arthritis was the Target Lesion Assessment Score. This score was determined for a single target lesion that was selected to be monitored throughout the trial. This measurement is a composite of four different evaluations: 1) plaque evaluation; 2) scaling; 3) erythrema; and 4) target lesion response to treatment. The following scale was used for the plaque elevation: 0=none (no evidence of plaque above normal skin level); 1=mild (slight but definite elevation above normal skin level); 2=moderate (moderate elevation with rounded or sloped edges to plaque); 3=severe (hard, marked elevation with sharp edges to plaque); 4=very severe (very marked elevation with very hard sharp edges to plaque). For the scaling assessment: 0=none (no scaling on the lesion); 1=mild (mainly fine scales, with some of the lesion at least partially covered); 2=moderate (somewhat coarser scales, most of the lesion at least partially covered); 3=severe (coarse, thick scales, virtually all the lesion covered, rough surface); 4=very severe (very coarse thick scales, all the lesions covered, very rough surface). For the erythema evaluation: 0=none (no erythema); 1=mild (light red coloration); 2=moderate (red coloration); 3=severe (very red coloration); 4=very severe (extreme red coloration). For target lesion response to treatment score: 0=completely cleared; 1=almost cleared (~90% improvement); 2=marked response (~75% improvement); 3=moderate response (~50% improvement); 4=slight response (~25% improvement); 5=condition unchanged; 6=condition worsened. The patient's Target Lesion Assessment Score was determined by summing the plaque, scaling, erythema and target lesion response scores for the monitored lesion. If the monitored lesion worsened, the percentage change from baseline was recorded as a negative number.

Treatment and placebo groups were compared in accord with the measurements described above, as well as for demographic and background characteristics; premature discontinuation rate; pain medication requirements; toxicities; serious adverse events; side effects reported by patients; number of weeks on drug until subjects met criteria for improvement, and response according to PsA subtype. Results were analyzed using standard statistical methods.

Dosing regimen

Recombinant human TNFR:Fc (etanercept) from Immunex Corporation was used in this study. The gene fragments encoding the etanercept polypeptides were expressed in a Chinese hamster ovary (CHO) expression vector.

TNFR:Fc was supplied as a sterile lyophilized powder containing 10 mg or 25 mg TNFR:Fc; 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg tromethamine (TRIS), USP per vial. Patients received either a dose of 25 mg of etanercept or a placebo. Vials of etanercept or identically-appearing placebo were reconstituted by aseptic injection of 1.0 mL Bacteriostatic Water for Injection, USP, (containing 0.9% benzyl alcohol), and was not filtered during preparation or prior to administration. If storage was required, the reconstituted solutions were stored at 2-8°C (36-46°F) in the original vial or in a plastic syringe for a period of no longer than 28 days. Dose was not changed during the study. Study drug was given twice weekly at approximately the same time of day.

Results

Study drug was well tolerated in all patients, and adverse events were consistent with this population and were equally distributed among both treatment groups. As illustrated in Tables 1-4, etanercept induced a significant improvement as compared with the placebo group in Psoriatic Arthritis Response (Table 1), ACR20 (Table 2), ACR50 (Table 3), PASI score, 50% improvement (Table 4), PASI score, 75% improvement (Table 5) and improvement in Target Lesion Assessment Score (Table 6). The fractions shown in Tables 1-5 represent numbers of patients. For example, the first entry in Table 1, which is "4/30," indicates that 4 of 30 patients in the placebo group scored as "improved" according to the Psoriatic Arthritis Response measurements. The tables include P-values for the differences between the two study groups, the groups being labeled as "PLACEBO" and "TNFR:Fc." All of the tables include data calculated after the first four weeks of the open label extension portion of the study ("EXTENSION"), during which *all* of the patients in both study groups received etanercept.

Table 1 shows the number of patients in each treatment group who scored as "improved" according to the Psoriatic Arthritis Response scoring system described above. By four weeks, there was a highly significant difference between etanercept and placebo groups. Moreover, after being switched to etanercept during the extension, those patients who had received placebo during the blinded portion of the study were seen to exhibit an

improvement over baseline (Table 1, Placebo, EXTENSION). These results indicate that etanercept acts rapidly to alleviate many aspects of psoriatic arthritis.

Table 1. Psoriatic Arthritis Response

	Placebo	TNFR:Fc	P-value
4 weeks	4/30 (13%)	23/30 (77%)	0.000
8 weeks	7/30 (23%)	25/30 (83%)	0.000
12 weeks	6/30 (20%)	26/30 (87%)	0.000
EXTENSION	17/23 (74%)	21/25 (84%)	0.356

Tables 2 and 3, respectively, illustrate the study results for the ACR20 and ACR50 endpoints. For either measure, a significant difference between etanercept and placebo groups was observed at all three time points during the blinded portion of the study. Given the differences between test and placebo groups after only four weeks of treatment (P=0.000 for ACR20 and P=0.011 for ACR50), these data suggest that notable improvement in ACR scores occurred within the etanercept group very soon after treatment was initiated, possibly after a single dose of etanercept. During the 4 week extension period, during which *all* of the patients received etanercept, a striking improvement in both ACR20 and ACR50 was seen in those patients who had received placebo during the first 12 weeks (Tables 2 and 3).

Table 2. ACR20 Response

	Placebo	TNFR:Fc	P-value
4 weeks	1/30 (3%)	18/30 (60%)	0.000
8 weeks	3/30 (10%)	19/30 (63%)	0.000
12 weeks	4/30 (13%)	22/30 (73%)	0.000
EXTENSION	11/23 (48%)	18/25 (72%)	0.093

Table 3. ACR50 Response

	Placebo	TNFR:Fc	P-value
4 weeks	0/30 (0%)	6/30 (20%)	0.011
8 weeks	1/30 (3%)	11/30 (37%)	0.001
12 weeks	1/30 (3%)	15/30 (50%)	0.000
EXTENSION	7/23 (30%)	11/25 (44%)	0.316

The results of the psoriasis evaluations are presented in Tables 4-6. Tables 4 and 5, respectively, present the numbers and percentages of patients in each group who exhibited a 50% or 75% improvement in PASI score, while Table 6 presents Target Lesion Assessment scores, these latter being denoted as percent improvement over baseline. The data in Tables 4-6 clearly indicate that etanercept induced an improvement in psoriasis for a large percentage of the patients who received it. When single lesions were evaluated (Table 6), the improvement in psoriasis was even more apparent than when PASI scores were used (Tables 4 and 5). It is notable also that, for either PASI scores (Tables 4 and 5) or Psoriasis Target Lesion Assessment Score (Table 6), the scores of the placebo group improved after these patients were switched to etanercept during the extension.

Though not shown in Table 6, Target Lesion Assessment Scores for patients who were concurrently receiving methotrexate (14 of the 30 patients in the etanercept group, and 14 patients in the placebo group) were compared with the scores of those patients who did not take methotrexate. Little difference in this index was noted between the patients who received methotrexate and those who did not receive it.

Table 4. PASI Score – 50% Improvement

	Placebo	TNFR:Fc	P-value
4 weeks	0/19 (0%)	4/19 (21%)	0.037
8 weeks	1/19 (5%)	7/19 (37%)	0.019
12 weeks	4/19 (21%)	8/19 (42%)	0.165
EXTENSION	6/16 (38%)	6/15 (40%)	0.856

Table 5. PASI Response Rate 75% Improvement

	Placebo	TNFR:Fc	P-value
4 weeks	0/19 (0%)	1/19 (5%)	0.264
8 weeks	0/19 (0%)	2/19 (11%)	0.153
12 weeks	0/19 (0%)	4/19 (21%)	0.037
EXTENSION	1/16 (6%)	4/15 (27%)	0.113

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Table 6. Psoriasis Target Lesion Assessment
(Percent Improvement or Worsening Compared with Baseline)

		Placebo	TNFR:Fc	P-value
4 weeks	Mean (SD)	2.7 (27.6)	21.2 (35.2)	0.120
	Median	0.0	14.3	
	MIN--MAX	-50.0 –50.0	-33.3 -100.0	
	N	19	19	
8 weeks	Mean (SD)	-7.5 (25.3)	28.5 (34.1)	0.003
	Median	0.0	29.2	
	MIN--MAX	-50.0 -20.0	-33.3 -100.0	
	N	17	18	
12 weeks	Mean (SD)	9.5 (23.2)	45.7 (31.6)	0.001
	Median	0.0	50.0	
	MIN--MAX	-25.0 -50.0	-16.7 -100.0	
	N	16	19	
EXTENSION	Mean (SD)	28.9 (41.2)	47.1 (35.8)	0.263
	Median	36.7	50.0	
	MIN--MAX	-100.0 -66.7	-33.3 -100.0	
	N	16	15	